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(54) Title: A METHOD OF MAKING PHARMACEUTICALLY ACTIVE TAXANES ORALLY BIOAVAILABLE

(57) Abstract

The present invention concerns a method of making pharmacologically active taxane compounds orally bioavailable. More particularly, the invention provides enhancing the oral absorption of pharmacologically active taxane compounds by co-administering a taxane with cinchonine.

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A METHOD OF MAKING PHARMACEUTICALLY ACTIVE TAXANES ORALLY BIOAVAILABLE

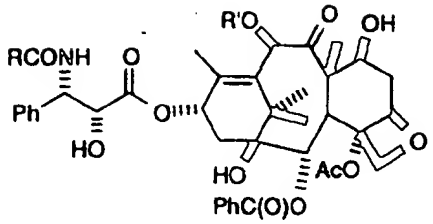
Field of the Invention

The present invention concerns a method of making pharmacologically active taxane compounds orally bioavailable. More particularly, the invention provides enhancing the oral absorption of pharmacologically active taxane compounds by co-administering a taxane with cinchonine.

Background Art

Taxol® (paclitaxel) is a natural product extracted from the bark of Pacific yew trees, Taxus brevifolia. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It has recently been approved for the treatment of refractory advanced ovarian cancer and breast cancer; and studies involving other cancers have shown promising results. The results of paclitaxel clinical studies are reviewed by numerous authors, such as by Rowinsky and Donehower in "The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics," Pharmac. Ther., 52:35-84, 1991; by Spencer and Faulds in "Paclitaxel, A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Potential in the Treatment of Cancer," Drugs, 48 (5) 794-847, 1994; and by K.C. Nicolaou et al. in "Chemistry and Biology of Taxol," Angew. Chem., Int. Ed. Engl., 33: 15-44, 1994, and also in the references cited therein.

A semi-synthetic analog of paclitaxel named Taxotere® (docetaxel) has also been found to have good antitumor activity. The structures of paclitaxel and docetaxel are shown below.



Taxol® (paclitaxel): R = Ph; R' = acetyl
Taxotere® (docetaxel): R = t-butoxy; R' = hydrogen

Oral bioavailability of paclitaxel or docetaxel is extremely low; thus, they are essentially orally inactive. (For example see Figure 2 which gives rat plasma concentration of paclitaxel given orally.) The drugs are administered intravenously. In a typical patient previously treated with chemotherapy for ovarian cancer, the recommended regimen for paclitaxel is 135 mg/m^2 or 175 mg/m^2 administered intravenously over three hours every three weeks. For a patient with carcinoma of the breast, the recommended dose for paclitaxel is 175 mg/m^2 administered intravenously over 3 hours every three weeks. (Physicians' Desk Reference, 49th Edition, 1995) Such intravenous infusion of paclitaxel (or any phamacologically active taxanes) makes the administration of the anticancer drug very inconvenient and expensive. Thus a method of making taxane more orally bioavailable would allow patient self-medication and thus increase convenience and reduce overall medical costs.

There have been attempts to enhance the oral activity of taxanes by first converting taxanes into prodrugs with the intent to enhance the oral absorption and thereafter delivering the free taxanes systemically. One such approach is described in European Patent Application No. 639577 published February 22, 1995. Without resorting to the prodrug method, we have now surprisingly discovered that orally administered paclitaxel co-administered with cinchonine significantly increases the oral bioavailability of paclitaxel. The mechanism of this action is not entirely understood.

SUMMARY OF THE INVENTION

The present invention concerns a method of making pharmacologically active taxane compounds orally bioavailable. More particularly, the invention provides making pharmacologically active taxane compounds orally bioavailable by co-administering a taxane with cinchonine. Another aspect of invention concerns a pharmaceutical formulation comprising a taxane and cinchonine. Yet another aspect of this invention relates to a method of orally administering a taxane with cinchonine to a patient in need of taxane.

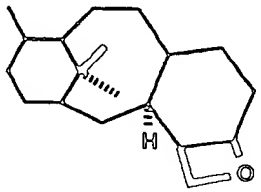
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Rat plasma paclitaxel concentration (ng/ml) after p.o. co-administration of paclitaxel (50mg/kg) and cinchonine (250 mg/kg).

Figure 2. Rat plasma paclitaxel concentration (ng/ml) after p.o. co-adminstration of paclitaxel (50mg/kg) and cinchonine (250 mg/kg), and paclitaxel (50mg/kg) p.o. administration alone.

DETAILED DESCRIPTION

The term pharmacologically active taxane compounds (or simply taxanes) which are co-administered with cinchonine refer to compounds with a diterpene framework of the structure:



They have inherent inhibitory effect with regard to abnormal cell proliferation, and have inherent therapeutic properties that make it possible to treat patients who have pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cellular proliferation of malignant or non-malignant cells in various tissues and/or organs, including, non-limitatively, muscle, bone and/or conjunctive tissues; the skin, brain, lungs and sexual organs; the lymphatic and/or renal system; mammary cells and/or blood cells; the liver, digestive system, and pancreas; and the thyroid and/or adrenal glands. These pathological conditions can also include psoriasis; solid tumors; ovarian, breast, brain, prostate, colon, stomach, kidney, and/or testicular cancer, Kaposi's sarcoma; cholangiocarcinoma; choriocarcinoma; neuroblastoma; Wilm's tumor, Hodgkin's disease; melanomas; multiple myelomas; chronic lymphocytic leukemias; and acute or chronic granulocytic lymphomas. The taxanes in accordance with the invention are particularly useful in the treatment of non-Hodgkin's lymphoma, multiple myeloma, melanoma, and ovarian, urothelial, oesophageal, lung, and breast cancers. The taxanes can be utilized to prevent or delay the appearance or reappearance, or to treat these pathological conditions. In addition, the taxanes are useful in treating and/or preventing polycystic kidney diseases (PKD) and rheumatoid arthritis. Naturally, pharmacologically active taxanes encompass species such as paclitaxel or docetaxel.

Specific Embodiment

In one specific embodiment, paclitaxel and cinchonine, a cinchona alkaloid, were coadministered orally at 50 and 250 mg/kg, respectively. These two drugs were solubilized in the same dosing solution (10% EtOH, 10% Cremophor EL, and 80% water) yielding concentrations of 8 and 40 mg/ml for paclitaxel and cinchonine, respectively. The resultant paclitaxel plasma AUC's (area-under-the-curve) were 20-40 times higher (Fig. 1) in three rats when cinchonine was co-administered compared to historical data when paclitaxel was administered alone. These results have since been confirmed in a head-to-head comparison with paclitaxel dosing alone (Fig. 2). The

mechanism of this enhancement by cinchonine is not entirely understood.

The present invention concerns a method of increasing oral absorption of pharmacologically active taxane compounds, i.e. increasing the orally bioavailability, in mammals including humans. More particularly, the invention provides making pharmacologically active taxane compounds orally bioavailable by co-administering a taxane with cinchonine. By co-administering a taxane with cinchonine, it is intended that cinchonine be administered orally or parenterally, either simultaneously or non-simultaneouly with oral taxane administration. For example, this invention also encompasses a method of increasing bioavailability of taxanes by intravenous administration of cinchonine before or after the oral administration of a taxane compound. However, the preferred method is simultaneous oral administration of a taxane and cinchonine to a mammal, such as a human patient, in need of such taxane.

When taxane and cinchonine is co-administered, they can be in separate formulations or in the same formulation. Thus another aspect of invention concerns a pharmaceutical formulation (composition) comprising a taxane, cinchonine and one or more pharmaceutically acceptable exipients designed for the purpose of enhancing the oral absorption (and hence, the bioavailability.) Typical of pharmaceutically acceptable exipients are, for example, manitol, urea, dextrans, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid. The pharmaceutical formulation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

The doses of cinchonine and pharmacologically active taxane utilized to implement the methods in accordance with the invention

are the ones that make it possible to administer prophylactic treatment or to evoke a maximal therapeutic response. The doses vary, depending on the type of administration, the particular product selected, and the personal characteristics of the subject to be treated. In general, the doses are the ones that are therapeutically effective for the treatment of disorders caused by abnormal cell proliferation. The actual dose used will vary according to the particular composition formulated, the route of administration, and the particular site, host and type of disease being treated. Many factors that modify the action of the drug will be taken into account in determining the dosage including age, weight, sex, diet and the physical condition of the patient. In general the preferred dose of cinchonine and pharmacologically active taxane is independently 1 to 500 mg/kg per administration to a mammal, including a human patient, in need of such taxane.

What is claimed is:

1. A method of enhancing oral absorption of a pharmacologically active taxane to a human in need of such taxane whereby the taxane is co-administered with cinchonine.

2. A method as claimed in 1 in which cinchonine is co-administered orally.

3. A method as claimed in claim 2 in which cinchonine is co-administered orally and simultaneously with the taxane.

4. A method as claimed in claims 1-3 in which the taxane is paclitaxel.

5. A method as claimed in claims 1-3 in which the taxane is docetaxel.

6. A method as claimed in claim 3 in which the taxane is paclitaxel.

7. A method as claimed in claim 6 in which paclitaxel is given 50 mg/kg, and cinchonine is orally administered at 250 mg/kg.

8. A pharmaceutical formulation (composition) comprising a taxane, cinchonine, and one or more pharmaceutically acceptable exipients.

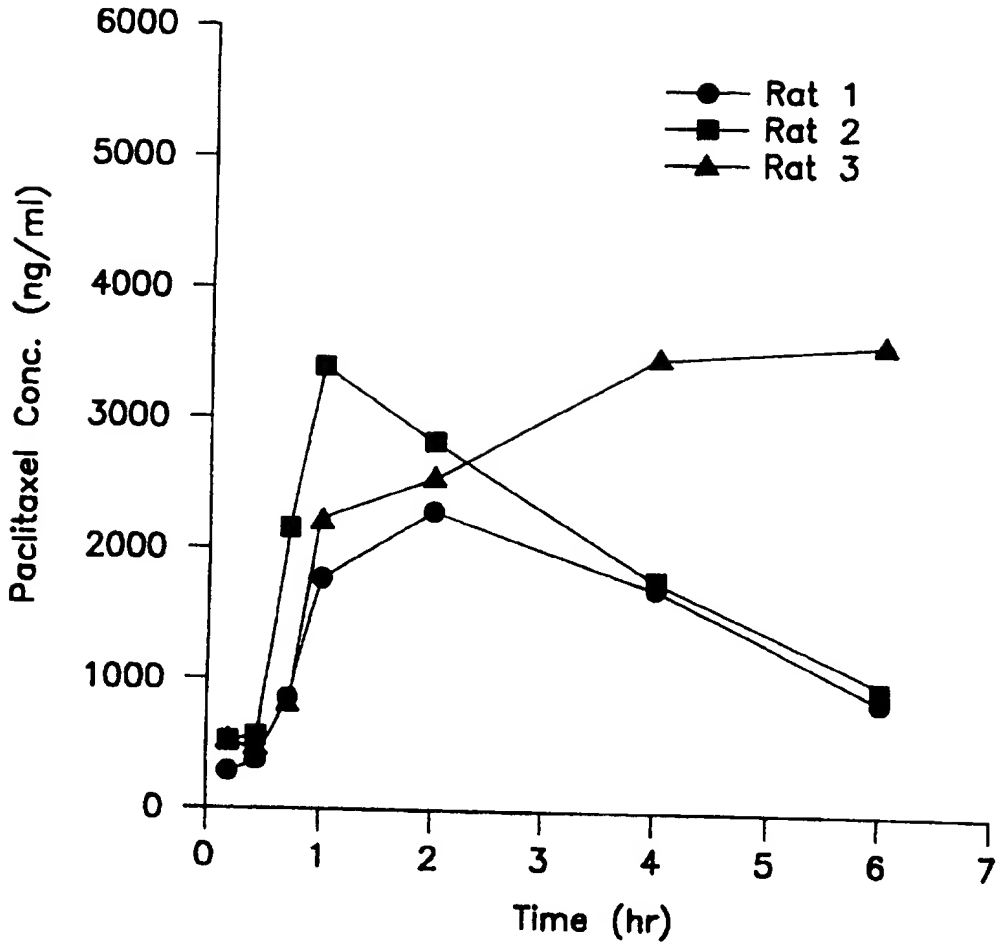

6000
5000
4000
3000
2000
1000
0
Paclitaxel Conc. (ng/ml)
0
1
2
3
4
5
6
7
Time (hr)
Rat 1
Rat 2
Rat 3

FIG. 1

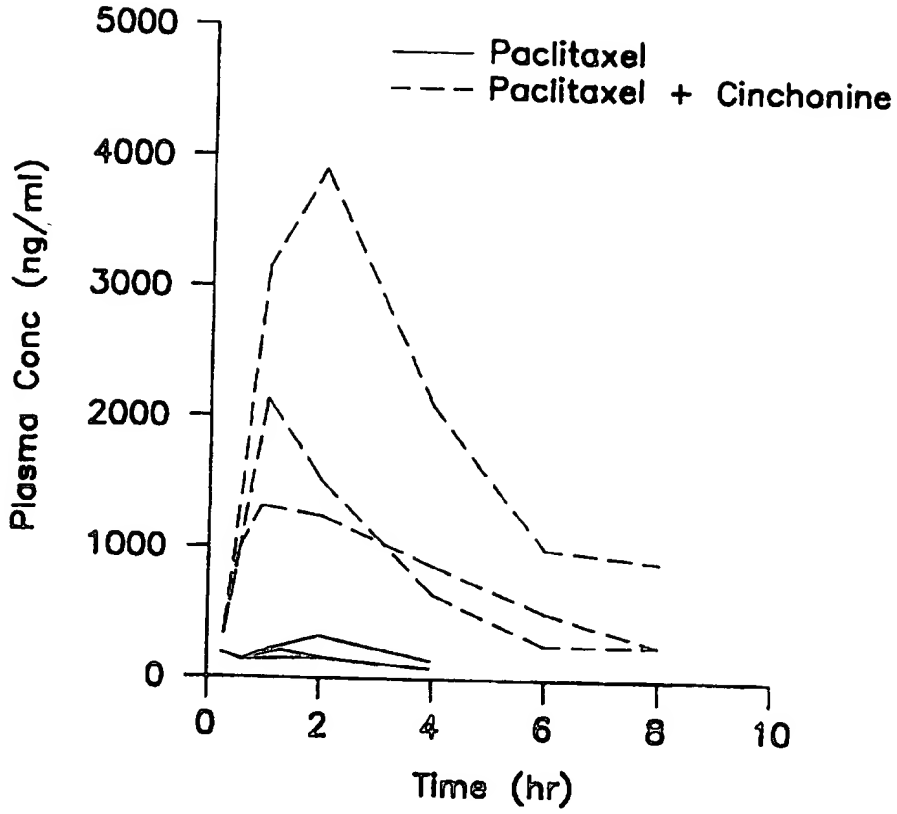

5000
4000
3000
2000
1000
0
Plasma Conc (ng/ml)
0
2
4
6
8
10
Time (hr)
Paclitaxel
Paclitaxel + Cinchonine

FIG. 2

International application No.
PCT/US97/00405

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/44, 31/47

US CL : 514/278, 311

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/278, 311

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0,639,577 A1 (BRISTOL-MYERS SQUIBB COMPANY) 22 February 1995, see the entire patent.	1 and 3-8
Y	M. WINDHOLZ et al., "THE MERCK INDEX" published 1983 by Merck & Co., Inc. (Rahway, NJ, USA), page 324, abstract no. 2262, see entire abstract.	1, 2, 7 and 8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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